ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Clinical features and brain MRI volumetric changes in anti-mGluR5 encephalitis

Yueqian Sun[1,2], James X. Tao[3], Xiong Han[4], Xiangqing Wang[5], Yulan Zhu[6], Yajun Lian[7], Guoping Ren[1,2] & Qun Wang[1,2,8]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]National Center for Clinical Medicine of Neurological Diseases,Beijing, China
[3]Department of Neurology, The University of Chicago, Chicago, USA
[4]Department of Neurology, Henan Provincial People's Hospital, Zhengzhou, China
[5]Department of Neurology, Chinese PLA General Hospital, Beijing, China
[6]Department of Neurology, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China
[7]Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
[8]Collaborative Innovation Center for Brain Disorders, Beijing Institute of Brain Disorders, Capital Medical University, Beijing, China

Correspondence
Qun Wang and Guoping Ren, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No. 119 South 4th Ring West Road, Fengtai District, Beijing 100070, China. E-mail: wangq@ccmu.edu.cn (Q. W.); E-mail: renguoping6655@sina.com (G. R.)

Funding information
The study was financially supported by the National Key Program of China grant (2022YFC2503800 and 2017YFC1307500), the Capital Health Research and Development of Special grants (2016-1-2011 and 2020-1-2013), and the Beijing Natural Science Foundation (7232045 and Z200024).

Received: 11 April 2023; Revised: 24 May 2023; Accepted: 3 June 2023

***Annals of Clinical and Translational Neurology* 2023; 10(8): 1407–1416**

doi: 10.1002/acn3.51831

Abstract

Background: Anti-metabotropic glutamate receptor 5 (mGluR5) encephalitis is a rare and under-recognized autoimmune encephalitis. This study is conducted to characterize its clinical and neuroimaging features. **Methods**: Twenty-nine patients with anti-mGluR5 encephalitis (15 new cases identified in this study and 14 previously reported cases) were included in this study and their clinical features were characterized. Brain MRI volumetric analysis using FreeSurfer software was performed in 9 new patients and compared with 25 healthy controls at both early (≤6 months of onset) and chronic (>1 year of onset) disease stages. **Results**: The common clinical manifestations of anti-mGluR5 encephalitis included cognitive deficits (n = 21, 72.4%), behavioral and mood disturbances (n = 20, 69%), seizures (n = 16, 55.2%), and sleep disorder (n = 13, 44.8%). Tumors were observed in 7 patients. Brain MRI T2/FLAIR signal hyperintensities were observed predominantly in mesiotemporal and subcortical regions in 75.9% patients. MRI volumetric analysis demonstrated significant amygdala enlargement in both early and chronic disease stages compared to healthy controls ($P < 0.001$). Twenty-six patients had complete or partial recovery, one remained stable, one died and one was lost to follow-up. **Conclusion**: Our findings demonstrated that cognitive impairment, behavioral disturbance, seizures, and sleep disorder are the prominent clinical manifestations of anti-mGluR5 encephalitis. Most patients showed a good prognosis with full recovery, even in the paraneoplastic disease variants. The amygdala enlargement in the early and chronic disease stages is a distinct MRI feature, which exploratively offer a valuable perspective for the study of the disease processes.

Introduction

Autoimmune encephalitis (AE) consists of a group of noninfectious autoimmune inflammatory diseases affecting the central nervous system (CNS). AE was initially referred as "limbic encephalitis" by Corsellis et al. in 1968,[1] and the first case series of AE was reported by Vitaliani et al. in 2005.[2] Dalmau et al.[3] subsequently identified cases of anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis, contributing to the symptomatology of AE. Besides, AE are not limited to limbic encephalitis and can involve any part of the CNS and also the peripheral nervous system. In recent years, an increasing number of antigens have been identified as autoantibody targets linked to AE. These include intracellular antigens Hu, Yo, Ri, glutamic acid decarboxylase 65-kD (GAD 65), and collapsin response-mediator protein 5 (CV2/CRMP5),[4–7] and neuronal cell-surface antigens NMDAR,

leucine-rich glioma-inactivated 1 (LGI1),[8] γ-aminobutyric acid receptor (GABAR), a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and so on.[3,9,10] These two groups have different clinical features, cancer association and response to immunotherapy. The rapidly advancing knowledge of autoantibodies and their associated syndromes has created a fledging new field of autoimmune neurology with many unaddressed questions regarding their symptomatology, serological and neuroimaging features as well as long-term outcomes.[11]

Metabotropic glutamate receptors (*mGluRs*) are a family of *G*-protein-coupled receptors with widespread expression in the CNS. Eight genes coding for these receptors (*mGluR1* through *mGluR8*) have been cloned thus far.[12] Historically, these genes have been categorized into three groups based on sequence homology, pharmacology, and signal transduction mechanisms.[13] The Group 1 mGluRs consist of *mGluR1* and *mGluR5*, and almost locate exclusively on postsynaptic membrane. They critically modulate synaptic transmission, plasticity, and adaptive behaviors.[14] Studies in genetic and pharmacological animal models have demonstrated that *mGluR5* plays an important role in learning and memory in the hippocampus.[15,16]

Recently, anti-mGluR5 encephalitis has been identified as a new type of AE. There have been only a few (14) sporadic cases reported in the literature,[15–21] and therefore its clinical features including epidemiology, symptomatology, and prognosis remain poorly characterized. Brain MRI T2/FLAIR signal hyperintensities have been observed in some of these 14 patients, mainly in the mesiotemporal cortex, but may also involving parieto-occipital cortex, thalamus, pons, and cerebellum. It remains unclear whether there are MRI volumetric changes in patients with anti-mGluR5 encephalitis, as they have been observed in other limbic autoimmune encephalitis at early and chronic phases of the disease.[22]

Here, we embarked a multicenter study and identified the cohort of 15 new patients. We aimed to characterize the clinical features of anti-mGluR5 encephalitis in all 29 patients available so far including the 15 new cases and 14 previously reported cases. We further performed the MRI volumetric analysis in the early and chronic stages of anti-mGluR5 encephalitis to assess its neuroimaging features.[23,24]

Methods

Identification of new patients with anti-mGluR5 encephalitis

Medical records were searched in five medical center including Beijing Tiantan Hospital, Henan Provincial Peoples Hospital, the Second Affiliated Hospital of Harbin Medical University, the Peoples Liberation Army General Hospital, and the First Affiliated Hospital of Zhengzhou University from January 2000 to September 2022 for patients who underwent serum and/or cerebrospinal fluid (CSF) auto-antibody detection via cell-based assays (CBAs; Euroimmun, Lübeck, Germany). Autoantibodies testing panel included, NMDAR, LGI1, contactin-associated protein-2 (CASPR2), GAD65, GABABR, AMPA, mGLUR5, dipeptidyl-peptide-like protein 6 (DPPX), CV2/CRMP5, and IgLON family member 5 (IgLON5). Fifteen new patients with anti-mGluR5 encephalitis were identified among the five centers. The study was approved by the medical ethical committees at the individual institutions, and written informed consent was obtained from all participants.

Literature search of previously reported cases

We conducted searches on the literature retrieval platforms PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and WanFang Data (http://www.wanfangdata.com.cn/) for articles up to July 2022 by using the title/abstract *keyword* contains "mGLUR5" or "metabotropic glutamate receptor 5" AND *keyword* contains "encephalitis". Reference screening was conducted by two experienced neurological doctors, YQS and GPR. A total of 14 published anti-mGluR5 encephalitis cases were identified.

Data extraction from new and previously reported cases

The clinical information was extracted from all 29 patients including 15 new cases and 14 previously reported cases, including demographics, prodromal symptoms, neurologic symptoms, tumors and autoimmune comorbidities. Laboratory data included serum and CSF analysis, brain MRI, whole-body ^{18}F-FDG PET and electroencephalogram (EEG) recordings. Neurologic disabilities were assessed using the modified Rankin Scale (mRS). Three authors (YQS, QW, and GPR) independently assessed the clinical data and mRS with disagreements resolved by consensus.

MRI studies and volumetric analysis

For the MRI volumetric analysis, seven patients were removed and causes are detailed in Data S1. Twenty-five sex- and age-matched healthy subjects without history of neuropsychiatric disorders were also enrolled for MRI volumetric analysis. All patients included and controls were from the same hospital and were scanned using the

same MRI machine and acquisition parameters (using a 3T Siemens Verio scanner with a T1-MPRAGE sequence [repetition time (TR) = 2300 msec, echo time (TE) = 2.53 msec, flip angle = 12°, slice thickness = 1 mm, no gap, voxel size = 1 × 1 × 1 mm]).

Patients were divided into two groups according to the time of MRI acquisition. The early group consisted of the earliest available MRI studies performed within half a year of the disease onset (hereafter referred to as "MRI group 1"; $n = 7$). The late group consisted of the MRI obtained after 12 months of disease onset (hereafter referred to as "MRI group 2"; $n = 5$). Patients with repeated MRI examinations were included in both groups. Disease onset was defined as the first occurrence of seizures, and/or psychiatric disturbances, and/or memory impairment.

MRI volumetric analysis were performed using *FreeSurfer 7.1* (see Data S1 for details).[23] A subfield volumetric analysis was then conducted for regions with statistically significant differences between subgroups. Additionally, to account for individual differences in brain development in the anti-mGluR5 encephalitis, FreeSurfer longitudinal stream was used to estimate individual longitudinal volume trajectories.

Statistical analyses

Descriptive statistics were used to summarize the demographic and clinical characteristics. Statistical group comparisons on volumetric MRI data were conducted using the two-sample independent t test based on a $P < 0.001$ not corrected for multiple comparisons due to the small sample size. An additional paired t test ($P < 0.001$, uncorrected) was performed on longitudinal *FreeSurfer* analyses of three patients with repeated MRI examinations.

Results

Clinical features of anti-mGluR5 encephalitis

We identified 15 new cases with anti-mGluR5 encephalitis (2 children and 13 adults) among the five centers. Their detailed clinical characteristics were shown in Table S1. Combined with the 14 previously reported cases, we characterized the clinical features of the 29 patients with anti-mGluR5 encephalitis (Table 1). The median age was 38 years and male/female ratio was 16/13. Figure 1A shows the distributions of the presence or absence of tumors in patients by age and sex.

Eighteen patients (62.1%) reported prodromal symptoms, including headache (10), weight loss (7), flu-like symptoms (5), skin rash (2), vomiting (2), diarrhea (2), and asthenia (2). Ten patients had fever either before (6) or after (4) the onset of neurological symptoms. Overall, the most common symptoms were cognitive impairment ($n = 21$, 72.4%), behavioral and mood disturbances

Table 1. Clinical features of 29 patients with anti-mGluR5 encephalitis.

	Number of patients	Percentage (%)
Demographics		
Median age at onset, years (IQR)	38 (19.5–61.5)	
Gender, male	16/29	55.2
Comorbidity		
Autoimmune disorders	2/29	6.9
Tumor (within 5 years before/after encephalitis onset)	7/29	24.1
Clinical features		
Prodromal symptoms	18/29	62.1
Decreased consciousness	9/29	31
Behavioral and mood disturbances	20/29	69
Cognitive deficits	21/29	72.4
Speech impairment	5/29	17.2
Sleep disorder	13/29	44.8
Seizures	16/29	55.2
Focal onset	8/29	27.6
Generalized onset	10/29	34.5
Epileptic state	3/29	10.3
Autonomic dysfunction	6/29	20.7
Abnormal movements	2/29	6.9
Central hypoventilation	1/29	3.4
Ataxia	3/29	10.3
Autonomic dysfunction	6/29	20.7
Dystonia	3/29	10.3
Cranial nerve involvement	5/29	17.2
Limb weakness	4/29	13.8
Limb numbness	2/29	6.9
CSF analysis		
CSF OCB or increased IgG index	16/27	59.3
CSF pleocytosis[1]	16/29	55.2
CSF protein (>30 mg/dL)	6/29	20.7
Abnormal brain MRI onset	17/29	58.6
Abnormal EEG	11/26	42.3
Immunotherapy	22/29	75.9
First-line immunotherapy (steroids, IVIg, PP)	22/29	75.9
Second-line immunotherapy	7/29	24.1
Outcome at last follow-up		
mRS 0–2	24/28	85.7
mRS 3–6	4/28	14.3
Relapse	4/29	13.8

AZA, azathioprine; CYC, cyclophosphamide; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; mGluR5, metabotropic glutamate receptor 5; MMF, mycophenolate mofetil; OCB, CSF oligoclonal bands; PP, plasmapheresis; WBC, white blood cells per mm^3.
[1]CSF pleocytosis indicates white blood cell count of more than five cells per mm^3.

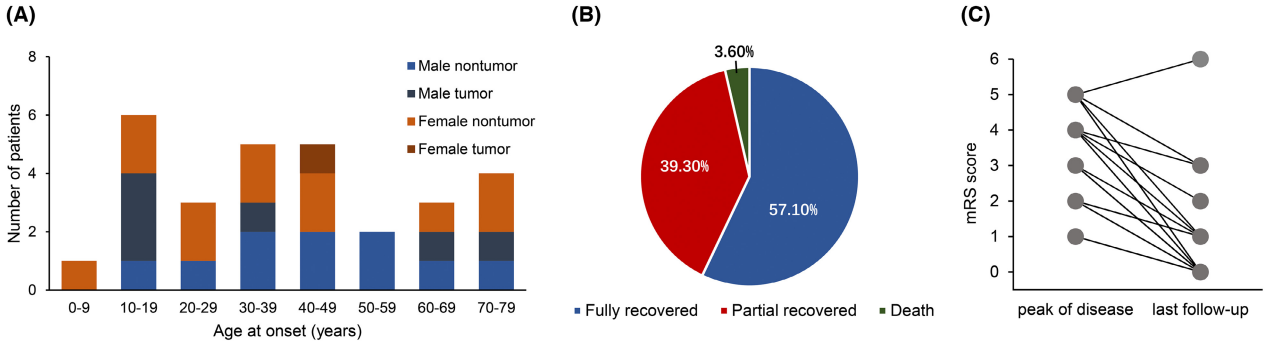

Figure 1. (A) The distributions of patients by age, sex, and the presence or absence of tumors. (B) The outcome at the last follow-up. (C) Comparison of mRS scores at peak of the disease with that at the last follow-up in 27 patients with available information.

(n = 20, 69%), seizures (n = 16, 55.2%), and sleep disorder (n = 13, 44.8%). The cognitive impairment was highlighted by memory decline and disorientation. Behavioral disturbances included irritability, apathy, aggression, manic, delusion, visual or auditory hallucinations, and bipolar mood. Of the cases with seizures, 6 developed generalized convulsive seizures (37.5%), 4 developed focal seizures (25%), 4 developed mixed generalized and focal seizures (25%), and 2 had unknown seizure type (12.5%). Three patients had status epilepticus. Sleep disorder included insufficient sleep (6), excessive daytime sleepiness (3), poor sleep quality (3), rapid eye movement (REM) sleep behavior disorder (2), and other sleep-related problems such as enuresis (1).

Other atypical or less common presentations included cranial nerve palsy, dystonia, dysarthria, limb weakness, numbness, autonomic dysfunction, and central hypoventilation. Cranial nerve palsy was observed in 5 (17.2%) patients, and cranial nerve VII was the most commonly affected cranial nerve (3/5), and other cranial nerve palsy included III (1/5) and X/XII (1/5). One patient had persistent left limb weakness as the first symptom. Tumors were reported in 7 patients including Hodgkin lymphoma (6) and small-cell lung cancer (1). Two patients were also diagnosed with systemic autoimmune diseases including Crohn's disease (1) and systemic lupus erythematosus (1).

Anti-mGluR5 antibody was detected in 21 patients in both serum and CSF, in 4 patients only in serum, and in 4 patients only in CSF. In those 21 patients who underwent serum and CSF antibody testing, 10 yielded a positive result in both serum and CSF, and 11 patients had positive results only for serum anti-mGluR5 antibody. Additionally, CSF study revealed leukocytosis in 55.2% patients, and positive oligo-clonal band (OCB) or increased IgG index in 59.3% patients. Almost half (42.3%) reported EEG abnormalities including diffuse and local slowing, spikes, sharp waves, spike and wave complex, and generalized epileptic polyspike bursts. Eleven patients underwent whole-body ^{18}F-FDG PET and brain hypometabolism was observed in 7 patients in the hippocampus (1), temporal lobe (1), both temporal lobe and hippocampus (4), temporoparietal cortex (2), and cerebellum (1).

Brain MRI findings and volumetric analysis

MRI was abnormal in 25/29 (86.2%) patients and in 17/29 (58.6%) patients at the disease onset. The most common abnormality was T2/FLAIR signal hyperintensity (n = 11, 37.9%) predominantly in the bilateral mesial temporal regions, but also observed in other cortical (frontal, parietal, and occipital lobes; insular and posterior cingulate cortex), subcortical (hippocampal, amygdala, and thalamic), and brainstem (pons) (Fig. 2). Other MRI abnormalities included leptomeningeal gadolinium enhancement (n = 2), non-specific small ischemic-like subcortical lesions (n = 2), cerebellar infarction (n = 1), and subdural effusion (n = 1). Ring-enhancing lesions and focal (e.g., hippocampus) and/or global atrophy were occasionally observed.

Volumetric analyses were performed in 9 patients (12 MRI studies) and 25 healthy controls (Fig. 3). Of the 9 patients, three have repeated MRI examinations at early and late phases of the disease. Overall, patients were divided into two groups according to the time of MRI acquisition (62 ± 64.63 vs. 506.6 ± 293.92 days). Comparative clinical data of patients and controls were illustrated in Table 2. FreeSurfer analysis revealed a significant amygdala volume enlargement in MRI group 2 compared with the control group (P < 0.001 uncorrected). Significant volume changes were not found in other cortical or subcortical regions except for white matter. No volumetric change was found overtime in hippocampal volume. Given the significant amygdala enlargement, we further analyzed the amygdala subfield volumes. The amygdala was automatically segmented and divided into nine

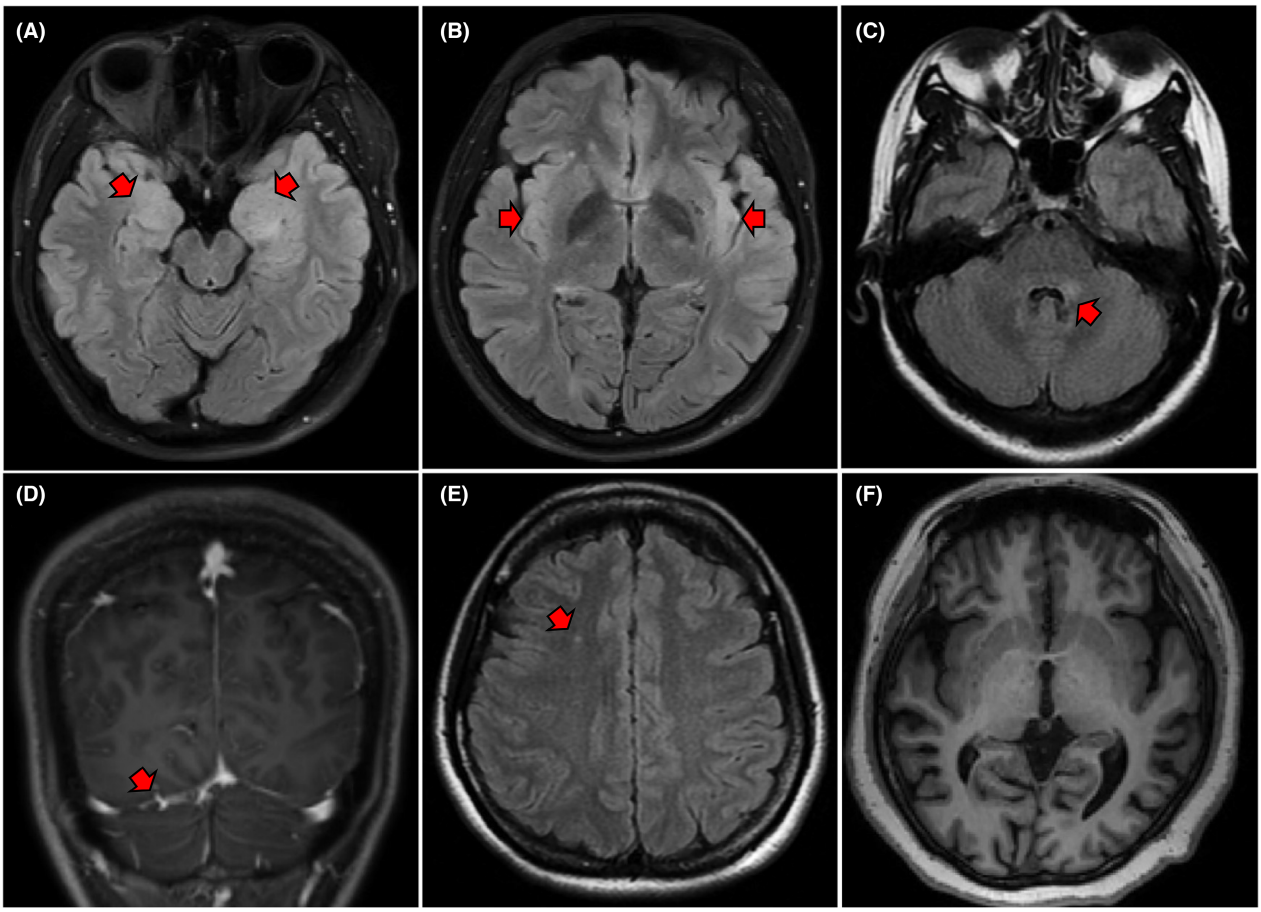

Figure 2. Neuroimaging features of routine MRI studies in anti-mGLUR5 encephalitis. (A) T2/FLAIR hyperintensities in the bilateral medial temporal lobes including both amygdala and hippocampus. (B) T2/FLAIR hyperintensities in bilateral insular lobes. (C:) T2/FLAIR hyperintensity in left brachium pontis. (D) Mild enhancement in the right tentorium cerebelli. (E) Small punctuate white matter T2/FLAIR hyperintensity in the right frontal lobe in a 30-year-old patient. (F) Global atrophy in T1 sequence in a 46-year-old patient.

nuclei, including the lateral, basal, accessory-basal nucleus (ABN), anterior-amygdaloid area (AAA), central, medial, cortical, cortico-amygdaloid transition (CAT), and paralaminar nucleus. All subsequent analyses were performed for both left and right amygdala. For MRI group 1, the enlargements of the right ABN, right CAT, left lateral nucleus, left basal nucleus, and left CAT, were statistically significant compared to controls; for MRI group 2, enlargements of the right lateral nucleus, right ABN, and right CAT were observed compared to controls ($P < 0.001$ uncorrected) (Figure S1). A longitudinal volumetric analysis of three patients showed a significant decrease in right amygdala volume in MRI 2 compared to MRI 1 ($P < 0.001$ uncorrected) (Fig. 4).

Treatment and prognosis

Twenty-two patients were treated with first-line immunotherapy including immunoglobulin (IVIG), corticosteroids, and plasmapheresis (PP). Seven patients received additional second-line immunotherapy (rituximab, azathioprine, and mycophenolate mofetil). Of the 7 patients with tumors, 5 received both oncological therapy and immunotherapy, and 2 patients received only oncological therapy.

Patients were followed up for a median of 15 months (range 1–96) with the exception of one lost to follow-up, with a median mRS score of 1 (range 0–6), significantly decreasing from the peak of the disease (Fig. 1B and C). One patient died due to cardiorespiratory failure caused by pulmonary infection. Four patients with Hodgkin lymphoma had a relapse of encephalitic symptoms after oncological therapy during the posttreatment follow-up at 3, 16, 30, and 48 months, respectively. Three of the 4 patients received additional immunotherapy (brentuximab) and autologous stem cell transplantation. All four patients showed significant improvement in their clinical symptoms.

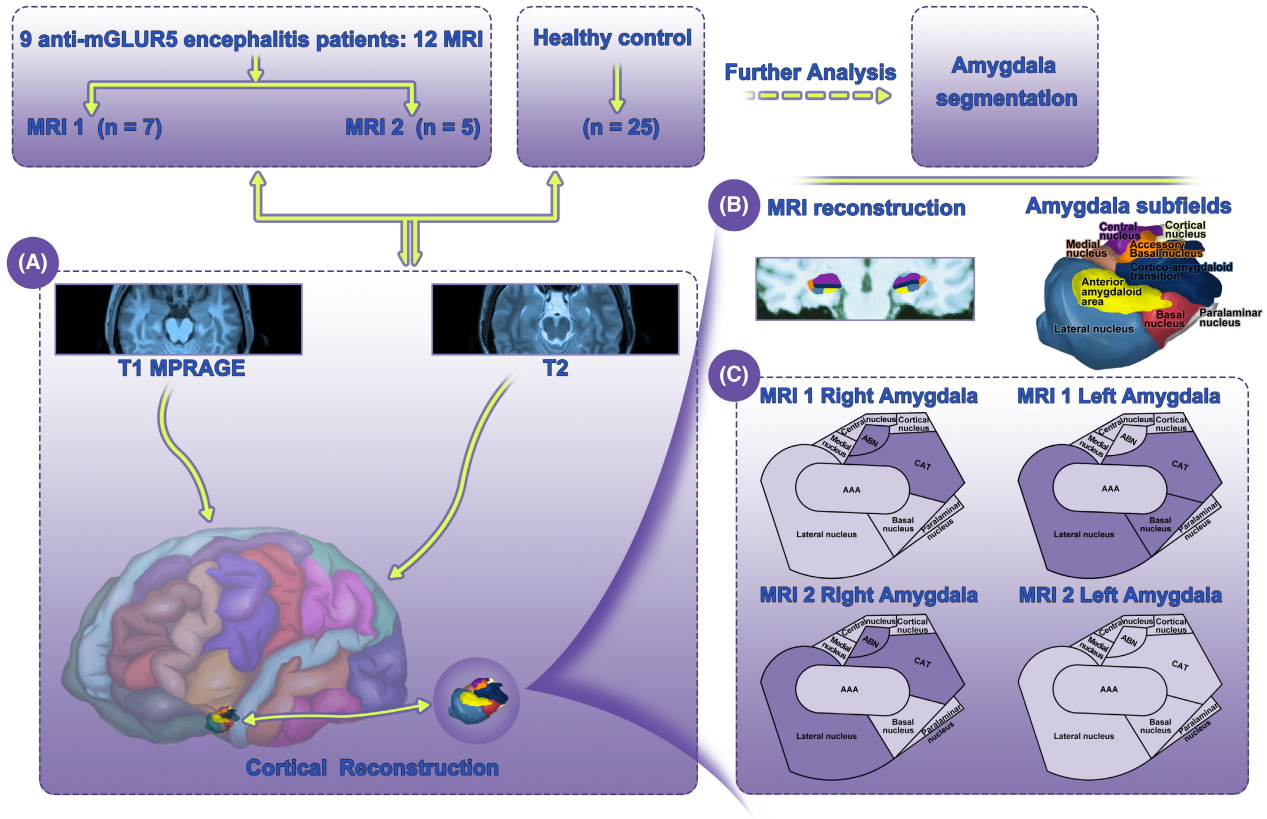

Figure 3. Schematic outline of MRI volumetric analysis. Nine patients (12 MRI studies) and 25 healthy subjects were included in the analysis. (A) Neuroimage pre-processing including cortical reconstruction of T1-MPRAGE images and co-registration of T2 images. (B) Amygdala segmentation. (C) Schematics depicting the amygdala subnuclei with dark purple representing a statistically significant increase in subnuclei volumes compared with healthy controls ($P < 0.001$, uncorrected). ABN, accessory-basal nucleus; AAA, anterior-amygdaloid area; CAT, cortico-amygdaloid transition.

Table 2. Brain volumes of the anti-mGluR5 encephalitis subgroups and the healthy control groups.

	Healthy controls	MRI 1		MRI 2	
	Volume	Volume	*P* value	Volume	*P* value
Global brain (mm^3)	1547442.78 ± 128742.33	1492281.68 ± 140773.05	0.334	1378453.30 ± 228365.01	0.026
Gray matter[1] (% brain)	4024.52 ± 229.49	4223.81 ± 403.06	0.098	4136.77 ± 409.18	0.391
White matter[1] (% brain)	3161.05 ± 184.06	2964.43 ± 212.83	0.022	2830.31 ± 113.3	<0.001*
Ventricular[1] (% brain)	115.62 ± 49.01	121 ± 61.05	0.809	174.76 ± 127.58	0.079
Thalamus[1] (% brain)	92.53 ± 7.52	92.26 ± 14	0.946	91.12 ± 7.41	0.706
Putamen[1] (% brain)	66.42 ± 10.15	75.28 ± 10.34	0.051	73.44 ± 11.35	0.177
Caudate nucleus[1] (% brain)	46.14 ± 6.31	50.64 ± 6.86	0.112	48.83 ± 3.21	0.366
Pallidum[1] (% brain)	29.67 ± 12	29.39 ± 2.96	0.952	26.67 ± 1.92	0.588
Hippocampus[1] (% brain)	46.87 ± 2.16	47.66 ± 4.9	0.529	49.85 ± 6.2	0.058
Amygdala[1] (% brain)	22.82 ± 1.21	26.26 ± 3.57	<0.001*	25.53 ± 3.88	0.006
Brainstem[1] (% brain)	139.26 ± 10.16	133.36 ± 88.23	0.174	137.8 ± 87.14	0.767
Cerebellum[1] (% brain)	868.61 ± 74.04	864.21 ± 95.24	0.897	950.34 ± 185.2	0.100

Data were presented as means ± SD. mGluR5, metabotropic glutamate receptor 5.
[1] ×10,000.
*$P < 0.001$ uncorrected.

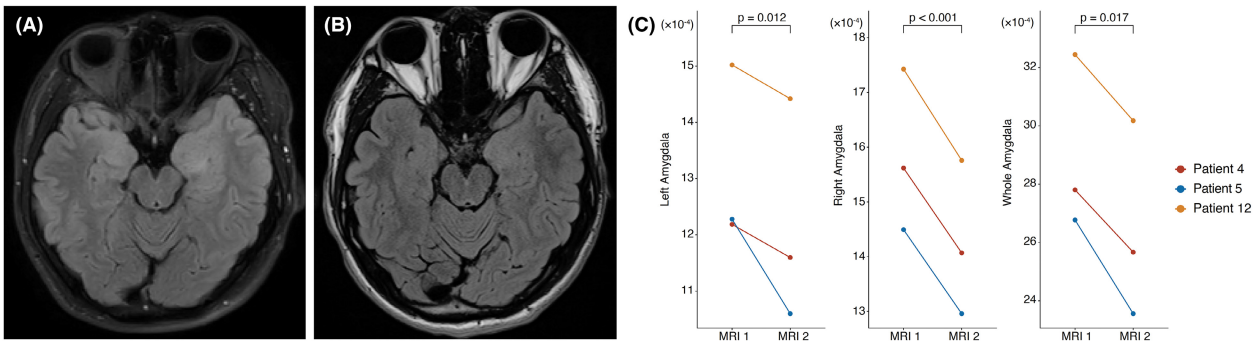

Figure 4. Longitudinal MRI volumetric analysis. (A) Amygdala enlargement in early study (MRI group 1) in Patient 4. (B) Decreased amygdala volume in late study (MRI group 2) in Patient 4. (C) Longitudinal analysis of three patients showed a significant decrease in right amygdala volume in MRI 2 compared to MRI 1.

Discussion

Anti-mGluR5 encephalitis is a rare type of AE, typically occurring in young adults with a median age of 38 years, albeit it can affect all age groups. In this study, we characterized the clinical features of anti-mGluR5 encephalitis in the 29 patients and demonstrated enlarged amygdala volume both in early and chronic stages that partially resolves during the course of the disease. These findings significantly expanded the clinical spectrum of anti-mGluR5 encephalitis.

The patients with anti-mGluR5 encephalitis have a pretty homogeneous presentation and some can have additional atypical symptoms. The vast majority of patients had mild and nonspecific prodromal symptoms. The main clinical manifestations included cognitive impairment, psychiatric disturbances, seizures, and sleep disorders. Atypical or less common presentations were also observed including cranial nerve palsy, dystonia, dysarthria, limb weakness and numbness, autonomic dysfunction, and central hypoventilation. These atypical presentations may lead to misdiagnosis and delayed treatment. These diverse clinical presentations are likely related to the ubiquitous expression of mGluR5 in various cortical and subcortical areas, such as the hippocampus, nucleus accumbens, dorsal striatum, and cerebral cortex.[25,26] Particularly, mGluR5 is highly expressed in hippocampus and amygdala that regulate mood and anxiety, stress responses, learning and memory processes,[15,27,28] which may contribute to cognitive and neuropsychiatric impairments. The seizure was a common presentation of anti-mGluR5 encephalitis and most patients had favorable seizure outcomes at the last follow-up. Sleep disorder was also a common presentation. Although sleep disturbance has been increasingly observed, it remains underrecognized in AE.[29,30] Unfortunately, polysomnography was not consistently obtained in this study, which likely underestimated the risk of sleep disorders in these patients with anti-mGluR5 encephalitis.

Overall, tumors were found in nearly one-fourth of patients, with the most common tumor to be Hodgkin's lymphoma. It appeared that there was a strong association between anti-mGluR5 encephalitis and Hodgkin lymphoma.[19] Nevertheless, all the tumor cases were found in previously reported cases, and none of 15 newly identified patients in this study had tumors. As such, we speculated that the incidence of tumors in patients with anti-mGLUR5 encephalitis may not be as high as initially reported. All 15 new patients were Asian ethnic background, whereas the previous reported 12 cases were Caucasian ethnic background. Different ethnic backgrounds may be contributory to the discrepancy, as we had reported in our previous studies of a multicenter AE cohort.[31] Besides, one might suspect differences in the detection methods that might lead to under-diagnosis of tumors in the current study, as only 11 of 15 patients underwent whole-body ^{18}F-FDG PET for tumor screening. Another possible explanation is that the duration of follow-up was shorter compared to previous series (median follow-up 15 vs. 48 months) and so the tumor detection frequency was lower. Tumors have been observed in long-term follow-up in patients with AE.[32] As such, oncological screening should be performed during long-term follow-up, particularly in those with relapsing anti-mGLUR5 encephalitis.[19]

Most patients had favorable outcomes at follow-up, and only a minority had poor outcomes. Several possible factors might be contributory to the unfavorable prognosis including concurrent CNS infection, poor seizure control, and complicated clinical course associated with pulmonary infetion.[33] Delayed diagnosis and treatment with immunotherapy may also lead to poor outcomes.[34]

In fact, two patients with poor prognosis had concurrent CNS infection in this study. To date, AE has been consistently reported at distance from infectious encephalitis by virus such as herpes simplex virus 1, Japanese encephalitis virus and HHV6, suggesting the development of neuronal autoimmunity triggered by viral infections, at distance from it. Also, antigen might remain detectable also when there is no more active infection, as it is the case for Cryptococcus meningitis. Aggressive treatment with antiviral agents and antibiotics in these high-risk patients might improve the prognosis. Some patients had a relapsing clinical course, and immunotherapy remained effective for the treatment of the relapse.

Brain MRI studies are important in the early diagnosis of AE. Similar to other AE, T2/FLAIR signal hyperintensities are commonly observed in the limbic and extra limbic structures such as cortex, thalamus, pons, and cerebellum in anti-mGluR5 encephalitis. Additionally, an increased volume of amygdala and white matter was also observed in the early and late disease stage, which gradually decreased during the course of the disease, reflecting a self-limited course of neuroinflammation. Resolution of edema associated with the inflammation is assumed to be a major contributory factor in variation in white matter volume, but the effects of inflammation on subsequent white matter tissue loss also need to be considered. Previous study has already demonstrated that inflammatory lesions are thought to be one of the foremost factors contributing to axonal loss in white matter tracts[35] and we speculate that white matter volume loss might be an important biomarker of this process. Studies suggested that the increased volumes of mesiotemporal structures in the initial phase of limbic encephalitis might reflect neurotoxicity or cytotoxic edema caused by loss-of-function of energy-dependent sodium-potassium adenosine triphosphatase.[36,37] Swollen amygdala on MRI and its decreased volume during follow-up imaging appear to be a sensitive marker for anti-mGluR5 encephalitis, and an early antibody-testing in serum and CSF should be pursued for an autoimmune etiology.[38] However, we focused on the volumetric changes in amygdala rather than in hippocampus, due to no statistical difference was found in hippocampal volume between the groups. Hippocampus is the main area involved in most AE, both clinically and radiologically. Low sample size may explain the results. In parallel, we need to highlight the sample size was limited, so the results should be considered exploratory.

The amygdala is a core area of limbic system involved not only in the control of positive and negative effects, but also in the modulation of neurocognitive functions.[39] It comprises multiple structurally and functionally distinct subnuclei. The basolateral complex of the amygdala (BLA) is a key brain region for the activity of corticosterone, which increases excitability in BLA projection neurons and reduces inhibition through GABA receptors,[40] and subsequently modulates neural plasticity and memory formation in the prefrontal cortex and the hippocampus.[41,42] Additionally, amygdala has been identified as a major component of epileptic focus in temporal lobe epilepsy, and it is used extensively in rodents as a site of stimulation in the kindling model of epilepsy.[43] As such, the significant volume changes of amygdala particularly in BLA subnuclei might account for the major clinical manifestations of anti-mGluR5 encephalitis.

There are several limitations in our study. First, although this study included all the 29 existing cases, it is still a small case cohort. The relative short period of follow-up also limited the assessment of long-term prognosis. Second, false-positive results may exist in our analysis, as the mGluR5 antibodies were tested using only one machine (CBAs rather than immunohistochemistry), and most were positive only in serum. Third, only 9 new cases were available for MRI volumetric analysis, and they were separated into early and late disease MRI groups, unfortunately leading to even lower sample size for each group. Besides, only three cases for the longitudinal volumetric analysis. In this regard, the findings in this study should be interpreted with caution and validated in the future studies, because the study was exploratory in nature.

Conclusion

Anti-mGLUR5 encephalitis is a rare autoimmune encephalitis with clinical manifestations mainly including behavioral disturbance, cognitive impairment, seizures, and sleep disorders. As it becomes increasingly recognized, additional symptoms are likely to be identified, particularly those atypical symptoms. Most patients respond to immunotherapy, and some may recover without the treatment. As an explorative MRI volumetric analysis, we also provided the evidence of amygdala swelling as a prominent neuroimaging feature in the early disease stage, which gradually resolved during the late stage of the disease. These findings further expanded the clinical knowledge of the disorder. Given the small cohort of cases known so far, future prospective and large cohort studies are warranted to further determine the clinical and neuroimaging features of this disease.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We would like to thank the participants in the study and their families.

Author contributions

Qun Wang and Yueqian Sun concepted, designed, and supervised the study. Yueqian Sun, Xiong Han, Xiangqing Wang, Yulan Zhu, and Yajun Lian acquired the data. Yueqian Sun analyzed and interpreted the data, provided statistical analysis, had full access to all of the data in the study, and are responsible for the integrity of the data and the accuracy of the data analysis. Yueqian Sun drafted the manuscript, Yueqian Sun, James X. Tao, Guoping Ren, and Qun Wang critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Conflict of interest

The authors report no competing interests.

Data availability statement

The data for this study are available through a request to the corresponding author.

References

1. Corsellis JA, Goldberg GJ, Norton AR. "Limbic encephalitis" and its association with carcinoma. Brain. 1968;91(3):481-496.
2. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol. 2005;58(4):594-604.
3. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61(1):25-36.
4. Dalmau J, Furneaux HM, Gralla RJ, Kris MG, Posner JB. Detection of the anti-Hu antibody in the serum of patients with small cell lung cancer--a quantitative western blot analysis. Ann Neurol. 1990;27(5):544-552.
5. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain. 2000;123(Pt 7):1481-1494.
6. McKeon A, Tracy JA. GAD65 neurological autoimmunity. Muscle Nerve. 2017;56(1):15-27.
7. Werry C, Götz F, Wurster U, et al. Paraneoplastic autoimmune encephalitis associated with CV2/CRMP-5 IgG antineuronal antibodies in a patient with thymoma. J Neurol. 2009;256(1):129-131.
8. Schultze-Amberger J, Pehl D, Stenzel W. LGI-1-positive limbic encephalitis: a clinicopathological study. J Neurol. 2012;259(11):2478-2480.
9. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009;65(4):424-434.
10. Tsuchiya H, Haga S, Takahashi Y, Kano T, Ishizaka Y, Mimori A. Identification of novel autoantibodies to GABA (B) receptors in patients with neuropsychiatric systemic lupus erythematosus. Rheumatology (Oxford). 2014;53 (7):1219-1228.
11. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391-404.
12. De Blasi A, Conn PJ, Pin J, Nicoletti F. Molecular determinants of metabotropic glutamate receptor signaling. Trends Pharmacol Sci. 2001;22(3):114-120.
13. Pin JP, Duvoisin R. The metabotropic glutamate receptors: structure and functions. Neuropharmacology. 1995;34 (1):1-26.
14. Scheefhals N, MacGillavry HD. Functional organization of postsynaptic glutamate receptors. Mol Cell Neurosci. 2018;91:82-94.
15. Mat A, Adler H, Merwick A, et al. Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. Neurology. 2013;80(14):1349-1350.
16. Lancaster E, Martinez-Hernandez E, Titulaer MJ, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology. 2011;77(18):1698-1701.
17. Prüss H, Rothkirch M, Kopp U, et al. Limbic encephalitis with mGluR5 antibodies and immunotherapy-responsive prosopagnosia. Neurology. 2014;83(15):1384-1386.
18. Guevara C, Farias G, Silva-Rosas C, et al. Encephalitis associated to metabotropic glutamate receptor 5 (mGluR5) antibodies in cerebrospinal fluid. Front Immunol. 2018;9:2568.
19. Spatola M, Sabater L, Planagumà J, et al. Encephalitis with mGluR5 antibodies: symptoms and antibody effects. Neurology. 2018;90(22):e1964-e1972.
20. Endian Guo JL, Hong Z. A case of anti-mGluR5 encephalitis. Chin J Nerv Ment Dis. 2021;47(1):44-47. (in Chinese).
21. Yueqiu Chen HG, Ligang X. A case report of anti-metabotropic glutamate receptor 5 encephalitis with extreme delta brush in electroencephalogram. Chin J Neurol. 2021;54(2):131-135. (in Chinese).
22. Wagner J, Witt JA, Helmstaedter C, Malter MP, Weber B, Elger CE. Automated volumetry of the mesiotemporal structures in antibody-associated limbic encephalitis. J Neurol Neurosurg Psychiatry. 2015;86(7):735-742.
23. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 1999;9(2):179-194.
24. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. Neuroimage. 1999;9(2):195-207.
25. Romano C, Sesma MA, McDonald CT, O'malley K, van den Pol AN, Olney JW. Distribution of metabotropic glutamate receptor mGluR5 immunoreactivity in rat brain. J Comp Neurol. 1995;355(3):455-469.

26. Shigemoto R, Nomura S, Ohishi H, Sugihara H, Nakanishi S, Mizuno N. Immunohistochemical localization of a metabotropic glutamate receptor, mGluR5, in the rat brain. Neurosci Lett. 1993;163 (1):53-57.
27. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. Cell. 2008;132 (4):645-660.
28. Janak PH, Tye KM. From circuits to behaviour in the amygdala. Nature. 2015;517(7534):284-292.
29. Muñoz-Lopetegi A, Graus F, Dalmau J, Santamaria J. Sleep disorders in autoimmune encephalitis. Lancet Neurol. 2020;19(12):1010-1022.
30. Ariño H, Muñoz-Lopetegi A, Martinez-Hernandez E, et al. Sleep disorders in anti-NMDAR encephalitis. Neurology. 2020;95(6):e671-e684.
31. Sun Y, Ren G, Ren J, et al. A validated nomogram that predicts prognosis of autoimmune encephalitis: a multicenter study in China. Front Neurol. 2021;12:612569.
32. Bost C, Chanson E, Picard G, et al. Malignant tumors in autoimmune encephalitis with anti-NMDA receptor antibodies. J Neurol. 2018;265(10):2190-2200.
33. Qiu X, Zhang H, Li D, et al. Analysis of clinical characteristics and poor prognostic predictors in patients with an initial diagnosis of autoimmune encephalitis. Front Immunol. 2019;10:1286.
34. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother. 2015;15 (12):1391-1419.
35. Brück W, Bitsch A, Kolenda H, Brück Y, Stiefel M, Lassmann H. Inflammatory central nervous system demyelination: correlation of magnetic resonance imaging findings with lesion pathology. Ann Neurol. 1997;42 (5):783-793.
36. Urbach H, Soeder BM, Jeub M, Klockgether T, Meyer B, Bien CG. Serial MRI of limbic encephalitis. Neuroradiology. 2006;48(6):380-386.
37. Bartsch T, Döhring J, Reuter S, et al. Selective neuronal vulnerability of human hippocampal CA1 neurons: lesion evolution, temporal course, and pattern of hippocampal damage in diffusion-weighted MR imaging. J Cereb Blood Flow Metab. 2015;35(11):1836-1845.
38. Lu YM, Jia Z, Janus C, et al. Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP. J Neurosci. 1997;17(13):5196-5205.
39. Pape HC, Pare D. Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. Physiol Rev. 2010;90(2):419-463.
40. Duvarci S, Paré D. Glucocorticoids enhance the excitability of principal basolateral amygdala neurons. J Neurosci. 2007;27(16):4482-4491.
41. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. Nat Rev Neurosci. 2009;10(6):423-433.
42. Richter-Levin G, Maroun M. Stress and amygdala suppression of metaplasticity in the medial prefrontal cortex. Cereb Cortex. 2010;20(10):2433-2441.
43. Aroniadou-Anderjaska V, Fritsch B, Qashu F, Braga MFM. Pathology and pathophysiology of the amygdala in epileptogenesis and epilepsy. Epilepsy Res. 2008;78(2–3):102-116.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplementary methods.
Table S1. Clinical features, antibody results, treatment and outcome of 15 patients with anti-mGluR5 encephalitis.
Figure S1. MRI volumetric analysis compared with healthy controls.

